EVIDENCE ON DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF FENBUTATIN OXIDE

REPRODUCTIVE AND CANCER HAZARD ASSESSMENT SECTION

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

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Fenbutatin Oxide

- Large organotin pesticide (MW 1052.7 D)
- Insoluble in water
- Somewhat soluble in aromatic solvents
- Used as miticide on fruits, vegetables, nuts, flowers
- Poorly absorbed orally: approximately 1% in rats, cows
- Acute toxicity: oral LD_{50} in rats 4400 mg/kg
- Chronic toxicity: typically reduced body weight (e.g. rats at 300 ppm in food)

Studies with possible evidence of developmental effects

- No human data
- Rat developmental study (Shell 1980b)*
- Dutch rabbit developmental studies A and B (Shell 1973a)
- New Zealand White rabbit developmental study (Shell 1981)*
- Rat reproductive study (3-gen., 2 litter/gen., male and female treated) (Hine Laboratories 1973)*
- Rat reproductive study (2-gen., 1 litter/gen., male and female treated) (du Pont 1990)

* cited by U.S. EPA

Rat developmental study (Shell 1980b)

- Mated Wistar rats treated at 0, 15, 30, or 60 mg/kg/d on gd 6-15 by gavage, sacrificed on gd 20

Effects observed:

- Reduced pregnancies at 30, 60 mg/kg/d (SS at 30, marginal SS at 60)
- Increased mean pre-implantation losses at 15, 60 mg/kg/d (SS at 60)
- No effect live fetuses/litter

Additional considerations:

- Implantation occurs on gd 5-6, treatment began gd 6
- No dose response of reduced pregnancies or mean pre-implantation losses
- “Negative” pre-implantation losses in some animals (more implants than corpora lutea counted)

Dutch rabbit developmental studies (Shell 1973a)

- Mated Dutch rabbits treated at 0, 3, or 10 mg/kg/d on gd 6-18 by capsule, sacrificed on gd 28 (Study A)

Effects observed:

- Increased resorptions plus early fetal deaths and fetuses with major abnormalities at 3, but not 10 mg/kg/d
- Large numbers of maternal deaths, apparently randomly distributed among groups

Additional considerations:

- Lack of dose-response for resorptions plus fetal deaths, abnormalities
- Lack of statistical analysis for resorptions plus fetal deaths, abnormalities

Dutch rabbit developmental studies (Shell 1973a)

- Mated Dutch rabbits treated at 0, 3, or 10 mg/kg/d on gd 6-18 by capsule, sacrificed on gd 29 (Study B)

Effects observed:

- Small, dose-related increase in resorptions plus early fetal deaths at 3 and 10 mg/kg/d
- No increase in major malformations
- Large numbers of maternal deaths, apparently randomly distributed among groups

Additional considerations:

- Lack of statistical analysis for resorptions plus fetal deaths

New Zealand White rabbit developmental study (Shell 1981)

- Mated New Zealand White rabbits treated at 0, 1, 5, or 10 mg/kg/d on gd 6-18 by capsule, sacrificed on gd 29

Effects observed:

- 10 mg/kg/d: increased maternal deaths (5/23), reduced maternal weight (SS), increased abortions (60%: SS), increased post-implantation losses (not SS), reduced number of litters with live fetuses (SS)
- 5 mg/kg/d: maternal deaths (2/18), increased post-implantation losses (not SS)
- 1 mg/kg/d: no maternal deaths or other effects
- 0 mg/kg/d: 2/18 maternal deaths

Additional considerations:

- Thalidomide positive control: no maternal deaths

3-gen. rat reproductive study (Hine Labs 1973)

- Male and female Long-Evans rats treated at 0, 50, 100, 300 ppm in food for 3 generations with 2 litters/generation

Effects observed:

- Small, consistent reduction in litter size at 300 ppm (SS for F1b only)
- Reduced postnatal survival (to day 21) at 300 ppm in F3a, F3b (SS)
- Reduced postnatal weight (day 21) at 300 ppm (SS 5/6 litters)
- Reduced parental weights at 300 ppm (SS male 3/3, female 2/3)

Additional considerations:

- Reduced litter size not observed in later rat reproduction study
- Exposure before developmental period
- Pups may have been exposed postnatally (milk, food)

2-gen. rat reproductive study (du Pont 1990)

- Male and female Sprague-Dawley rats treated at 0, 45, 75, 250, or 500 ppm in food for 2 generations with 1 litter/generation

Effects observed:

- Reduced postnatal weight gain at 500 ppm, F1 and F2 (SS)
- Reduced parental weight gain (male and female) at 500 ppm, P1 and F1 (SS)

Additional considerations:

- Exposure before developmental period
- Pups may have been exposed postnatally (milk, food)

Studies with possible evidence of female reproductive effects

- No human data
- Rat reproductive study (3-gen., 2 litter/gen., male and female treated) (Hine Laboratories 1973)
- Rat reproductive study (2-gen., 1 litter/gen., male and female treated) (du Pont 1990)
- Rat acute inhalation (IBTL 1972a, 1972b, 1972c)
- Rat, mouse, and dog chronic oral (Shell 1973b, 1973c, 1980a, U.S. EPA 1994)

No effects on fertility

- 3-generation rat reproductive study (Hine Labs 1973)
- 2-generation rat reproductive study (du Pont 1990)

No observations of ovarian gross or histopathological effects

- 2-generation rat reproductive study (du Pont 1990)
- Acute inhalation studies in rats (IBTL 1972a, 1972b, 1972c)
- Chronic studies in rats (Shell 1973b), mice (Shell 1980a, U.S. EPA 1994), or dogs (Shell 1973c)

Studies with possible evidence of male reproductive effects

- No human data
- Rat reproductive study (3-gen., 2 litter/gen., male and female treated) (Hine Laboratories 1973)
- Rat reproductive study (2-gen., 1 litter/gen., male and female treated) (du Pont 1990)
- Mouse dominant lethal study (Shell 1972)
- Rat acute inhalation (IBTL 1972a, 1972b, 1972c)
- Rat subchronic oral (SRI 1970)
- Rat, mouse, and dog chronic oral (Shell 1973b, 1973c, 1980a, U.S. EPA 1994)

Dominant lethal study in male mice (Shell 1972)

- Male mice treated at 0, 250, or 500 mg/kg once orally, mated with 3 untreated females each for one week, repeated for 8 weeks. Females examined on gd 13.

Effects observed:

- No adverse effects on number of pregnancies, total number of implants, early fetal deaths.

Additional considerations:

- Not clear if systemically toxic dose was used.

No effects on fertility

- 3-generation rat reproductive study (Hine Labs 1973)
- 2-generation rat reproductive study (du Pont 1990)
- Dominant lethal study in mice (Shell 1972)

No observations of testicular gross or histopathological effects

- 2-generation rat reproductive study (du Pont 1990)
- Acute inhalation studies in rats (IBTL 1972a, 1972b, 1972c)
- Subchronic study in rats (SRI 1970)
- Chronic studies in rats (Shell 1973b), mice (Shell 1980a, U.S. EPA 1994), or dogs (Shell 1973c)

Overview of rat testes weight effects

Inconsistent indications of increased testes weight in animals exposed when mature:

- Increased* absolute testes weight in 1-month study at 500, 1000 ppm
- Increased (SS) absolute testes weight at terminal sacrifice (24 months) in chronic study at 600 ppm
- No increase in absolute testes weight at 3, 6, or 12 months in chronic study to 600 ppm
- No increase in absolute testes weight after 18 weeks in P1 of 2-gen. to 500 ppm

Additional considerations

- Reduced body weight in all studies
- 15-week food restriction study (Chapin et al. 1993) in mature animals reduced to 90, 80, or 70% of control body weight:
  no change in absolute testes weight,
  increased relative testes weight due to reduced body weight

* Value calculated by OEHHA staff: SS not addressed

Overview of rat testes weight effects cont.

Indications of reduced testes weight in animals exposed during perinatal period:

- Reduced absolute* and relative (SS) testes weight in F3b weanlings (3 weeks old) at 100, 300 ppm in 3-gen.
- Reduced (SS) absolute testes weight, increased relative (SS) testes weight at term in F1 at 500 ppm in 2-gen.

Additional considerations

- Reduced body weight at 300 ppm in 3-gen., 500 ppm in 2-gen.

* Value calculated by OEHHA staff: SS not addressed

Summary: developmental

- Rat developmental study
  Reduced pregnancies, increased pre-implant losses
- Rabbit developmental studies (3)
  Increased post-implant losses, maternal deaths (random and dose-related)
- Rat 3-gen. study
  Reduced litter size, reduced postnatal growth and survival, reduced parental weight
- Rat 2-gen. study
  Reduced postnatal growth, reduced parental weight

Summary: female reproductive

- Rat 3-gen. study
  No effect fertility. Reduced litter size, reduced postnatal growth and survival, reduced parental weight
- Rat 2-gen. study
  No effect fertility. Reduced postnatal growth, reduced parental weight
- Rat, mouse, dog/acute, chronic
  No ovarian gross or histopathology

Summary: male reproductive

- Rat 3-gen. study
  No effect fertility. Reduced litter size, reduced parental weight
- Rat 2-gen. study
  No effect fertility, litter size. Reduced parental weight
- Mouse dominant lethal study
  No effect fertility, pre- or post-implantation losses
- Rat, mouse, dog/acute, subchronic, chronic, repro
  No testicular gross or histopathology
- Rat testes weight effects:
  mature: inconsistent increases in absolute testes weight
  perinatal: indications of reduced testes weight